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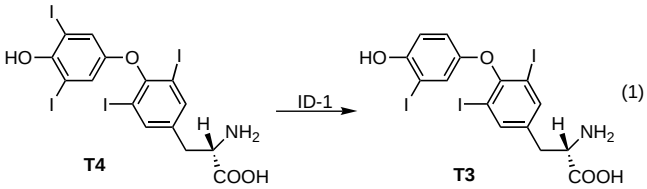
[14] Based on the chirality of the catalyst used to induce the asymmetry[13] in **4** and the rotation ($[\alpha]_D^{23} = -61°$, $c = 1\ mg\,mL^{-1}$, $CHCl_3$) of the synthetic natural product obtained from this intermediate, we tentatively assign the shown absolute stereochemistry of colombiasin A. Further studies to confirm this assignment are in progress.

Reactions of Organoselenenyl Iodides with Thiouracil Drugs: An Enzyme Mimetic Study on the Inhibition of Iodothyronine Deiodinase**

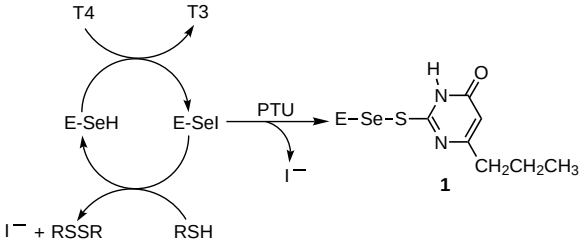
Wolf-Walther du Mont,* Govindasamy Mugesh, Cathleen Wismach, and Peter G. Jones

The monodeiodination of the prohormone thyroxine (**T4**) to the biologically active hormone 3,5,3′-triiodothyronine (**T3**) is the first step in thyroid hormone action and the type I iodothyronine deiodinase (ID-1), an enzyme containing selenocysteine in its active site, is responsible for most of this conversion [Eq. (1)].[1] ID-1 is an integral membrane



(1)

protein the highest amounts of which are found in the liver, kidney, and thyroid. The 5′-deiodination catalyzed by ID-1 is a ping-pong, bisubstrate reaction in which the selenol group of the enzyme (E-SeH) first reacts with thyroxine (**T4**) to form a enzyme selenenyl iodide (E-SeI) complex with release of deiodinated iodothyronine (**T3**). Subsequent reaction of the selenenyl iodide with an unidentified cytoplasmic thiol cofactor (possibly glutathione, GSH) releases I^- ions and regenerates the E-SeH active site (Scheme 1).[2]



Scheme 1. Proposed mechanism for iodothyronine deiodination of thyroxin **T4** by ID-1 and the inhibition of ID-1 by PTU.

It was proposed that the drug 6-*n*-propyl-2-thiouracil (PTU), derived from thiourea, inhibits the activity of the enzyme, probably by reacting with the selenenyl iodide intermediate to form a stable selenenyl sulfide.[2] The selenenyl sulfide **1** is considered to be a dead-end product since this compound does not react with thiols under physiological conditions. Owing to this property, PTU is often used in the treatment of severely hyperthyroid (Graves disease) patients and is therefore well known as an antithyroid drug.

The formation of a mixed selenenyl sulfide adduct (**1**, Scheme 1) in the reaction of the selenenyl iodide with PTU has been proposed mainly on the basis of the following assumptions. 1) The PTU inhibition is noncompetitive with respect to thyroxine and competitive with respect to thiol cofactor, which suggests that PTU and cofactor react with the same enzyme intermediate.[1a] 2) The thiouracil derivatives are particularly reactive towards protein sulfenyl iodide (S–I) groups[1a] and presumably even more reactive towards selenenyl iodide (Se–I) groups. However, since the discovery that the ID-1 is a selenium-containing enzyme, the reactions of thiourea drugs with E-SeI and their mechanisms have never been experimentally verified. In contrast to ID-1, the other two deiodinases (ID-2 and ID-3) are insensitive to PTU.[1c] It is, therefore, still a matter of debate as to whether PTU reacts with a covalent Se–I species or if it reacts with the enzyme active site (E-SeH). Moreover, no reasons have been given for the insensitivity of ID-2 and ID-3 towards PTU.[1c] Herein, we report the first model studies on the reactivity of PTU towards selenenyl iodides as a basis for the deiodinase inhibition.

The reactions of organoselenenyl iodides as enzyme-mimetic substrates with thiourea derivatives have not been studied previously as areneselenenyl iodides such as PhSeI are themselves generally unstable and disproportionate in solution.[3a] Even the sterically hindered areneselenenyl iodides such as **2** have been found to exist in equilibrium with iodine and the corresponding diselenide in solution.[3b,c] The "non-existence" of stable binary Se–I compounds is associated with the very similar electronegativities of Se and I, that is, the lack of ionic contribution to the resonance energy in the covalent Se–I bond.[4] However, the recent observations that the

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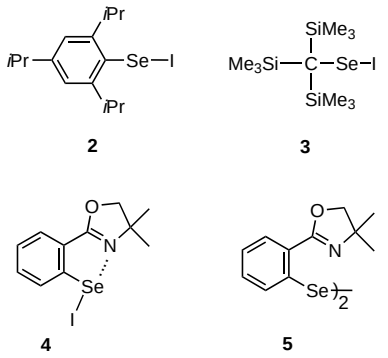
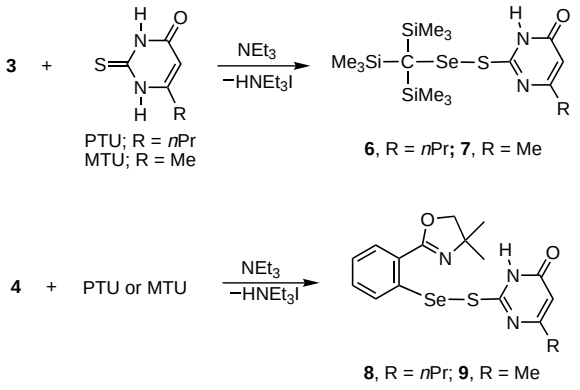
covalent Se–I bond could be stabilized against dismutation (disproportionation) reactions by introducing sterically highly demanding alkyl substituents[3a,d] (**3**) or internally chelating groups[5] (e.g. **4**) have given opportunities for studying the reactivity of pure Se–I compounds.



2 **3** **4** **5**

When "PhSeI" ($0.5\,Ph_2Se_2I_2$) and **2**, which are known to disproportionate to diselenide and iodine or their adducts,[3a,b] were treated independently with stoichiometric amounts of PTU or 6-methyl-2-thiouracil (MTU) in the presence of triethylamine, both the reactions afforded the corresponding diselenides, rather than the selenenyl sulfides, as the only products. This indicates that the unstable selenenyl iodides PhSeI and **2** are reduced by PTU and MTU to the corresponding diselenides (and not the PTU/MTU derivatives). These properties of PhSeI and **2** therefore resemble the inhibitory action of PTU-insensitive deiodinases.

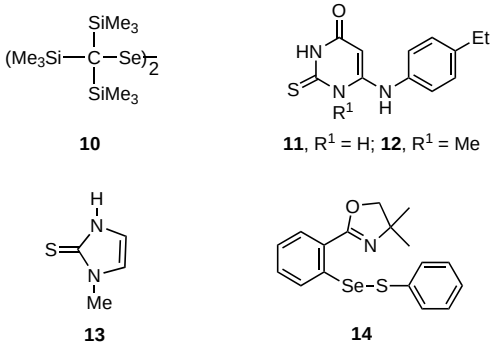
In the absence of triethylamine, selenenyl iodide **3** reacted with PTU and MTU much more slowly than the internally chelated compound **4**. Although compound **4** reacted rapidly with PTU and MTU under similar experimental conditions, it unexpectedly afforded the diselenide **5** as the major product. This result indicates that the HI produced during the reaction may act as a catalyst for the diselenide formation. However, in the presence of triethylamine, no diselenide is formed and both **3** and **4** reacted rapidly with PTU and MTU to give the desired selenenyl sulfides **6**–**9** (Scheme 2). Since the liberated HI in both cases was trapped with triethylamine the compounds **6**–**9** could be purified conveniently by column chromatography. Remarkably, the diselenides **5**[6] and **10**[7] did not react with PTU and MTU, which indicates that the



Scheme 2. Synthesis of the thiouracil derivatives.

ID-1 enzyme inhibition by PTU and MTU results from the specific reactivity of the Se–I bond towards these drugs.

The reactions of **4** with PTU and MTU were found to be faster than those of **3**, probably because of an increase in the electrophilic reactivity of selenium atom in compound **4** by Se···N interactions. Whereas the Se–I bond in compound **3** is a 2-center 2-electron (2c-2e) covalent bond, the Se–I bond in compound **4** can be considered as a result of Se···N interactions as part of a 3c-4e system. Therefore, the Se–I bond in **4** is thermodynamically stabilized (and also dismutation resistant) in isolated form and kinetically activated towards reactions with nucleophilic reagents. As suggested for the natural enzyme,[1c] the hydrogen atom attached to N1 of PTU and MTU plays an important role in the reactions. The replacement of the hydrogen atom at the N1 position by a methyl group normally produces inactive substances. For example, it has been reported that the 6-anilino-2-thiouracil **11** exhibits 85% inhibition towards human placenta deiodinase activity, but the N-methylated derivative **12** exhibits only 2% inhibition.[8] In agreement with this, the inactivity of



10 **11**, R^1 = H; **12**, R^1 = Me

13 **14**

methimazole (MMI) **13**, another commonly used anti-thyroid drug that inhibits thyroid peroxidase (TPO), towards ID-1 has been ascribed to the presence of a methyl substituent at the N1 position.[1a,c] We found that MMI reacts with selenenyl iodide **3**, in the presence of triethylamine, with a rate comparable to that of PTU and MTU, with deprotonation of the N3 atom.[9]

In the drug-induced deiodinase inhibition, the fast reaction between the inhibitors and selenenyl iodide intermediate (E-SeI) and the inactivity of the resulting selenenyl sulfide towards reducing agents such as GSH are the important factors that determine the potency of the drugs. In our model studies, although compounds **3** and **4** react with PTU, the stability of the resulting selenenyl sulfides **6** and **8** towards thiols differs considerably. The internally chelated compound **8** reacted rapidly with PhSH to form the selenenyl sulfide **14** (thiol exchange), whereas the sterically hindered derivative **6** was found to be unreactive towards PhSH after 24 h under identical experimental conditions. In this regard, the PTU-derivative **6** clearly differs from the MMI-derivative, which reacts readily with PhSH leading to a thiol-exchange reaction.[9]

Although the "steric protection" is much more efficient than the internal chelation in stabilizing the selenenyl sulfides

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against further reaction with thiols, the existence of hydrogen bonding in the PTU-derivative **6** enhances its stability towards thiols. The absence of such hydrogen bonding in the MMI-derivative may be the reason for the inactivity of MMI towards ID-1 inhibition.[9] The X-ray crystal structure of compound **6** shows that the selenium atom is considerably shielded by the $SiMe_3$ groups (Figure 1).[10] The thiouracil moiety in **6** exists in a keto form that is stabilized by intermolecular hydrogen bonding, thus forming a centrosymmetric dimer.

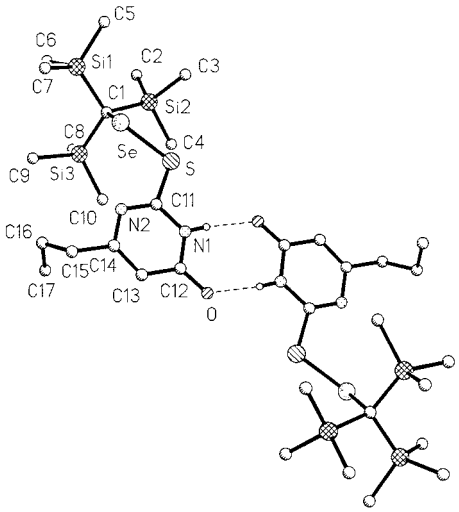

Figure 1. Molecular structure of **6** showing hydrogen bonding (only the H atom involved in hydrogen bonding is shown). Selected bond lengths [Å] and angles [°]: Se-S 2.2014(4), Se-C1 2.0043(15), S-C11 1.7681(16), C1-Si1 1.9270(15), C1-Si2 1.9130(15), C1-Si3 1.9042(16), C12-O 1.2398(18); C1-Se-S 105.91(4), C11-S-Se 103.78(5), Si1-C1-Se 99.84(7), Si2-C1-Se 110.34(7), Si3-C1-Se 108.29(7).

The higher reactivity of compound **8** with PhSH, compared with that of **6**, may also be attributed to the intramolecular Se···N interaction in compound **8**, which increases the electrophilic character of selenium center. This observation led us to investigate whether the PTU derived selenenyl sulfide **8** can be prepared from **14** which, as a result of internal chelation, should be activated towards nucleophilic attack. When pure **14**[11] was treated with PTU, we were unable to detect any **8** even after 24 h. Our observations indicate that the formation of **14** by thiol exchange from **8** with PhSH is an irreversible process.

In summary, the mechanism for the inhibition of iodothyronine deiodinase by thiourea based drugs is experimentally verified by utilizing two selenenyl iodides as enzyme-mimetic substrates (E-SeI) stabilized by steric protection or internal chelation. This model study supports the assumptions that 1) PTU does not react with the native enzyme but only with an E-SeI intermediate containing a covalent Se–I bond and 2) some basic amino acid residues such as histidine near the active center may kinetically activate the Se–I bond, or these residues may act as general bases for the abstraction of HI during the inhibition. This study also suggests that the possible disproportionation of the E-SeI intermediate to diselenides may, at least partially, account for the insensitivity of certain selenium-containing deiodinases towards thiourea drugs.

Experimental Section

General: All reactions were carried out under nitrogen using standard vacuum-line techniques.

6: NEt_3 (2 mmol) and PTU (0.17 g, 1 mmol) were added to a solution of **3** (0.44 g, 1 mmol) in toluene (20 mL). The mixture was stirred at room temperature for 10 min, and the resulting turbid solution was separated by filtration. After removal of the solvent from the filtrate, the crude product was loaded onto a silica gel (70–230 mesh) column, elution with hexane:ethylacetate (2:1) afforded **6** as the second yellow fraction which was collected and evaporated to dryness to give a yellow solid, crystallization from CH_2Cl_2:hexane to afford yellow crystals of **6** (0.41 g, yield 85%); m.p. 104 °C; ^{1}H NMR (400 MHz, C_6D_6, TMS): $\delta = 0.10$ (s, 27H), 0.58 (t, 3H), 1.37 (m, 2H), 2.02 (t, 2H), 5.80 (s, 1H), 6.97 (s, 1H); ^{13}C NMR (100.6 MHz, C_6D_6, TMS): $\delta = 1.36$, 2.93, 13.58, 21.19, 39.32, 109.45, 159.16, 163.67, 168.85; ^{77}Se NMR (38.2 MHz, C_6D_6, Me_2Se): $\delta = 506$; ^{29}Si NMR (39.8 MHz, C_6D_6, TMS): $\delta = 3.4$; CI-MS: *m/z* (%): 481 (100) [$M^+ - H$], 188, 171, 90; elemental analysis calcd (%) for $C_{17}H_{36}N_2O_2SSeSi_3$: C 42.50, H 7.50, N 5.83, S 6.67; found: C 42.93, H 7.78, N 5.48, S 6.81. Compounds **7**–**9** were synthesized by similar procedures.

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[9] The facile reaction of **3** with MMI/NEt_3 indicates that it is not the different reactivities of MMI and the thiourea derivatives PTU and MTU towards the E-SeI intermediate that control the different degrees of ID-1 inhibition but the difference in the reactivities of the resulting selenenyl sulfides. This is clearly connected with the fact that the MMI derived selenylsulfide does not possess any N–H and/or –N(H)C(=O)– groups for hydrogen bonding. The complete study of the reactivity of MMI towards Se–I bonds, the reactions of the resulting selenenyl sulfides with thiols, and their relevance to the natural systems will be discussed in the forthcoming full paper.

[10] Crystal data for **6** ($C_{17}H_{36}N_2OSSeSi_3$): $M_r = 479.77$, triclinic, space group $P\bar{1}$, $a = 9.2050(10)$, $b = 9.6540(10)$, $c = 14.0974(14)$ Å, $\alpha = 99.181(3)$, $\beta = 98.911(3)$, $\gamma = 91.627(3)°$, $V = 1220.0(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.306$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 153$ K; yellow prisms, crystal dimensions $0.40 \times 0.17 \times 0.07$ mm, crystals mounted in inert oil. Intensity data was collected by using the ω method in the 2θ range 5–60°. Of 20640 reflections collected on a Bruker SMART 1000 CCD diffractometer, 7049 were unique ($R_{int} = 0.0486$) and used for all calculations. After absorption correction (multiple scan) the structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically on F^2 using full-matrix least-squares to give $R_1 = 0.0344$, $wR_2 = 0.0794$ ($I > 2\sigma(I)$); $R_1 = 0.0406$,

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$wR_2 = 0.0822$ (all data). The NH proton was refined freely, methyl H atoms as rigid, and other H atoms as a riding model. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154120. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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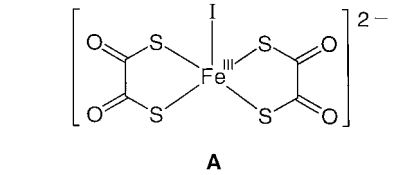
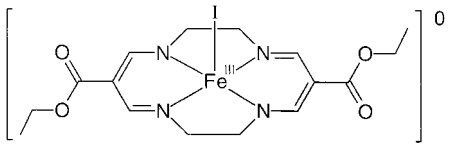
Tuning the Electronic Structure of Halidobis(*o*-imino-benzosemiquinonato)-iron(III) Complexes**

Hyungphil Chun, Thomas Weyhermüller, Eckhard Bill, and Karl Wieghardt*

Mononuclear complexes of iron(III) (d^5) containing redox-inert, closed-shell ("innocent") ligands adopt either a high-, intermediate-, or low-spin electron configuration: $S_{Fe} = 5/2$, $3/2$, or $1/2$, respectively. An increasing number of non-heme, pentacoordinate, pure intermediate-spin complexes have in recent years been characterized by X-ray crystallography, magnetic susceptibility measurements, Mössbauer, and electron paramagnetic resonance (EPR) spectroscopy.[1] Examples pertinent to this work are complexes **A**[1f] and **B**.[1d]



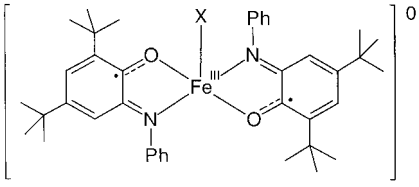
A



B

The binding of a Fe^{III} ion to open-shell ("noninnocent"), π-radical ligands such as phenoxyls[2a] or *o*-benzosemiquinonates[2b] inevitably induces a strong intramolecular, antiferromagnetic spin coupling between the magnetic orbitals of the π radicals and the available metal-centered, half-filled t_{2g} orbitals of the Fe^{III} ion. This gives rise to electronic ground states ranging from $S_t = 2$[2a,b] to $S_t = 0$[2c] depending on the number of coordinated radicals and the actual local spin state at the Fe^{III} ion in a given compound. *O,N*-coordinated *o*-aminophenolates have been shown to be readily oxidized by air to yield the corresponding *o*-iminobenzosemiquinonates, $(L^{ISQ})^-$.[3, 4] The octahedral complex $[Fe^{III}(L^{ISQ})_3]$ possesses an $S_t = 1$ ground state comprising a high-spin Fe^{III} ion ($S_{Fe} = 5/2$) coupled antiferromagnetically to three $(L^{ISQ})^-$ π-radical ligands.[3b]

We have now discovered that the pentacoordinate halidobis(*o*-iminosemiquinonato)iron(III) complexes **1**–**3** are readily prepared and that the local spin state of the respective Fe^{III} ion is tuned from a high-spin state in the chloro species **1** to a pure intermediate-spin state in the iodo complex **3**; in the bromo analogue **2** both spin isomers are present in the cystalline state in a 1:1 ratio. The crystal structures of **1**, **2**, and **3** have been determined with high precision by X-ray crystallography at 100 K. Figure 1 shows the structure of **3** (the structures of **1** and **2** are very similar and not shown); Table 1 summarizes selected bond lengths.



X = Cl, Br, I
trans-$[Fe(L^{ISQ})_2Cl]$ **1**
trans-$[Fe(L^{ISQ})_2Br]$ **2**
trans-$[Fe(L^{ISQ})_2I]$ **3**

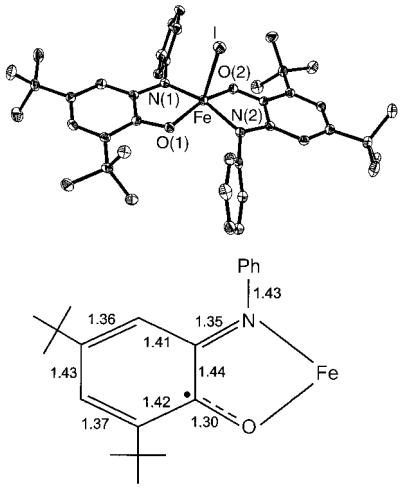


Figure 1. Structure of a neutral molecule in crystals of **3** ($S_t = 1/2$; top). The average C–C, C–O, and C–N bond lengths of the *o*-iminobenzosemiquinonate(1 –) π-radical ligand in **1**, **2**, and **3** are shown below. The estimated error is ±0.01 Å (3σ).

Table 1. Selected bond lengths [Å] in **1**, **2**, **3**, and [Fe("N_2S_2")I].[c]

	Fe–X	Fe–N(1)	Fe–N(2)	Fe–O(1)	Fe–O(2)
$[Fe^{III}(L^{ISQ})_2Cl]$ **1**	2.2203(7)	2.042(2)	2.041(2)	1.962(1)	1.964(1)
$[Fe^{III}(L^{ISQ})_2Br]$ **2**[a]	2.3665(9)	1.897(4)	1.886(4)	1.869(3)	1.877(3)
$[Fe^{III}(L^{ISQ})_2Br]$ **2**[b]	2.3694(9)	2.045(4)	2.050(4)	1.950(3)	1.953(3)
$[Fe^{III}(L^{ISQ})_2I]$ **3**	2.5912(5)	1.885(2)	1.885(2)	1.869(1)	1.881(1)
[Fe("N_2S_2")I][6]	2.5552(9)	1.842(4)	1.851(5)	2.181(2)[c]	2.188(2)[c]

[a] Molecule 1. [b] Molecule 2. [c] Fe–S bond length.

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